Synthesis and Evaluation of Novel Alkylpiperazines as Potential Dopamine Antagonists

Richard A. Glennon,* John J. Salley, Jr.,

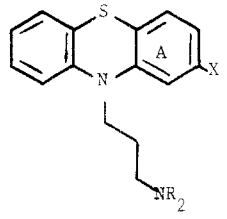
Department of Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298

Odd S. Steinsland, and Sharon Nelson

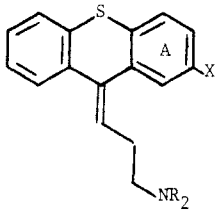
Department of Pharmacology and Toxicology, University of Texas, Medical Branch, Galveston, Texas 77550.
Received August 25, 1980

Several alkylpiperazines, monocyclic subfragments of known tricyclic neuroleptic agents, were evaluated as dopamine antagonists in the isolated rabbit ear artery preparation. Compounds prepared and evaluated are of the general structure Ar-X-$(CH_2)_n$-Y, where X = C, O, and N, n = 1-3, and Y, for the most part, was 4-methylpiperazine. Those compounds where X = NH, n = 3, and X = (*Z*)-CH=CH, n = 2, with an electron-withdrawing group meta to the side chain, possess dopamine antagonist activity comparable to that of clozapine. It is concluded that the entire tricyclic structure of phenothiazine-like agents (or at least more than a monocyclic ring system) is necessary for optimal activity as a dopamine antagonist in the receptor preparation used in this study.

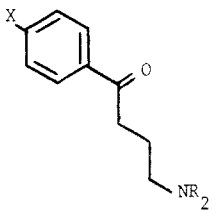
A role for the putative neurotransmitter dopamine has been implicated in the etiology of Parkinsons disease[1] and, more recently, in certain types of schizophrenias[2] as well as in affective disorders.[3] Although there is no direct evidence that dopamine plays a role in various types of psychoses, a dopaminergic mechanism is indirectly supported by a large body of pharmacological evidence.[4] Neuroleptic agents such as the phenothiazines (1), thioxanthenes (2), and butyrophenones (3) are known to suppress many of the symptoms associated with certain psychoses and, in addition, many of these compounds elicit Parkinson-like extrapyramidal stimulation as an undesirable side effect. Although it has been suggested that these two opposing effects result from the interaction of neuroleptic agents with different dopamine-sensitive receptors in the limbic forebrain and substantia nigra,[5] more recent evidence has shown that dopamine receptors in these two brain areas may be similar.[6] Nevertheless, all of these observations could be accounted for, at least in part, by a direct blockade of dopamine receptors.



1



2



3

Snyder and co-workers,[6,7] using calf brain homogenates, have demonstrated a correlation between the dopamine receptor binding affinities of a series of neuroleptic agents and their average clinical daily dose (i.e., neuroleptic potency). Similar results have been reported by Steinsland and Hieble using a rabbit ear artery preparation.[8] From these and other data, it has been postulated that neuroleptic drugs may exert their antipsychotic effects by blocking dopamine receptors. Crystallographic,[9] solution proton magnetic resonance,[10] and molecular orbital[11] investigations, as well as studies on conformationally restricted dopamine analogues,[12] indicate that dopamine exists in a trans conformation with the aryl and amine substituents being antiperiplanar. It has been proposed that the A ring of the phenothiazines (1) and thioxanthenes (2) interact with dopamine receptors in the same manner as the aryl ring of dopamine and that the side-chain nitrogens interact in a congruous manner with an amine site. Solid-state measurements of interfunctional group distances support this hypothesis.[10]

Following these criteria, the question might be raised as to whether the intact ring system of 1 and 2 is necessary for dopamine antagonism or whether antagonism resides in a smaller subfragment of these tricyclic molecules. For example, as a class, the butyrophenones, which lack the tricyclic structure of 1 and 2, are not only potent neuroleptic agents[13] but are also potent dopamine antagonists.[7] This paper describes the synthesis and evaluation of several simple compounds which might be viewed as molecular subfragments of the tricyclic compounds 1 and 2.

(1) (a) Hornykiewicz, O. *Annu. Rev. Pharmacol. Toxicol.* **1977**, *17*, 545. (b) Hornykiewicz, O. *Adv. Neurol.* **1975**, *9*, 445.
(2) (a) Crow, T. J.; Johnstone, E. C.; Longden, A.; Owen, F. *Adv. Biochem. Psychopharmacol.* **1978**, *19*, 301. (b) Carlsson, A. *Biol. Psychiatry* **1978**, *13*, 3.
(3) Laverty, R. *Prog. Neurobiol.* **1974**, *3*, 31.
(4) (a) Horn, A. S.; Korf, J.; Westerink, B. H. C., Eds "The Neurobiology of Dopamine"; Academic Press: London, 1979. (b) Sedvall, G.; Bjerkenstedt, L.; Lindstrom, L.; Wodehelgodt, B. *Life. Sci.* **1978**, *23*, 425.
(5) Anden, N.; Stock, G. *J. Pharm. Pharmacol.* **1973**, *25*, 346.
(6) Snyder, S. H. *Am. J. Psychiatry* **1976**, *133*, 197.
(7) (a) Creese, I.; Burt, D.; Snyder, S. H. *Science* **1976**, *192*, 481. (b) Burt, D.; Creese, I.; Snyder, S. H. *Mol. Pharmacol.* **1976**, *12*, 800.
(8) (a) Steinsland, O. S.; Hieble, J. P. *Science* **1978**, *199*, 443. (b) Steinsland, O. S.; Furchgott, R. F.; Kirpekar, S. M. *Circ. Res.* **1973**, *32*, 49.
(9) Bergin, R.; Carlstrom, D. *Acta Crystallogr., Sect. B.* **1968**, *24*, 1506.
(10) Horn, A. S.; Post, M. L.; Kennard, O. *J. Pharm. Pharmacol.* **1975**, *27*, 553.
(11) Kier, L. B. *J. Theor. Biol.* **1973**, *40*, 211.
(12) (a) Cannon, J. G.; Lee, T.; Goldman, H. D.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1977**, *20*, 1111. (b) Cannon, J. G.; Gutierrez, C. S.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341.
(13) (a) Fielding, S.; Lal, H., Eds. "Neuroleptics"; Futura: Mount Kisco, NY, 1974. (b) Kumar, N.; Jain, P. C. *Prog. Drug Res.* **1977**, *21*, 409.

0022-2623/81/1824-0678$01.25/0

Scheme I

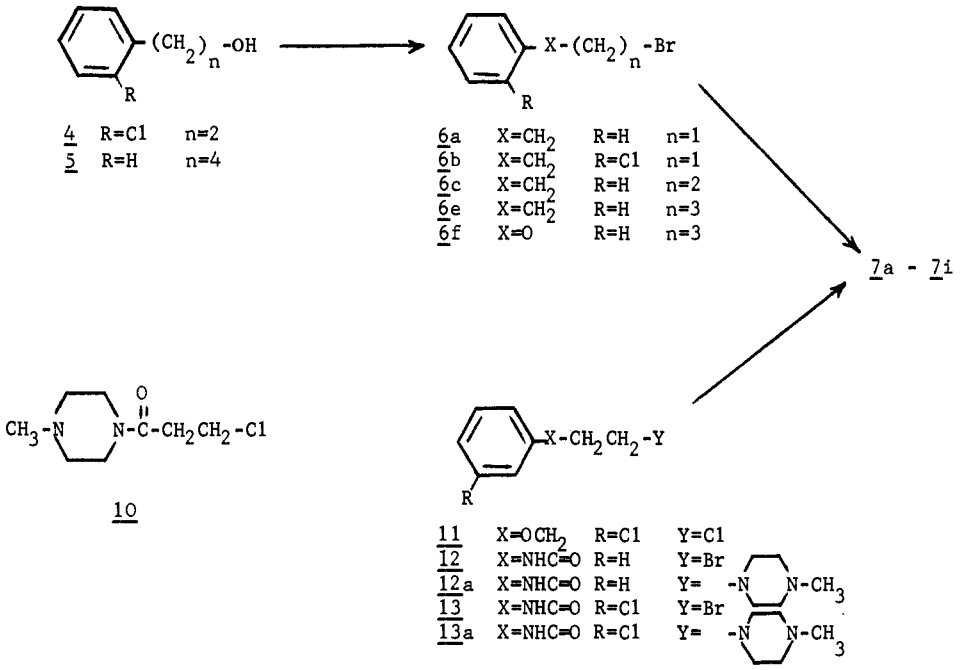
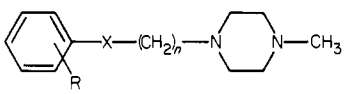
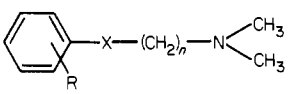


Table I. Properties of Test Compounds



7a-m



7n-p

no.	R	X	*n*	mp,[a] °C	% yield	recryst solvent	method of prepn[b]	formula[c]
7a	H	CH_2	1	279-280	97	abs EtOH	A	$C_{13}H_{20}N_2 \cdot 2HCl$
7b	2-Cl	CH_2	1	271-274	76	abs EtOH	A	$C_{13}H_{19}ClN_2 \cdot 2HCl$
7c	H	CH_2	2	261-264	85	abs EtOH	A	$C_{14}N_{22}N_2 \cdot 2HCl$
7d	2-Cl	CH_2	2	245-248	68	abs EtOH	B	$C_{14}H_{21}ClN_2 \cdot 2HCl$
7n	H	CH_2	2	129-131[d,e]	74	95% EtOH	C	
7o	2-OMe	CH_2	2	148-150[f]	76	EtOH/Et_2O	C	
7p	3-OMe	CH_2	2	122-124	75	EtOH/Et_2O	C	$C_{12}H_{19}NO \cdot HCl$
7e	H	CH_2	3	258-260	85	abs EtOH	A	$C_{15}H_{24}N_2 \cdot 2HCl$
7f	H	O	3	241-245	78	abs EtOH	A	$C_{14}H_{22}N_2O \cdot 2HCl$
7g	3-Cl	O	3	245-248	43	abs EtOH	D	$C_{14}H_{21}ClN_2O \cdot 2HCl$
7h	H	NH	3	210-212[d]	81	gl HOAc	E	$C_{14}H_{23}N_3 \cdot 3C_2H_2O_4 \cdot H_2O$
7i	3-Cl	NH	3	222-223[d]	85	gl HOAc	E	$C_{14}H_{22}ClN_3 \cdot 3C_2H_2O_4$
7j	H	(*Z*)-CH=CH	2	235-238	92	abs EtOH	A	$C_{15}H_{22}N_2 \cdot 2HCl \cdot 0.5H_2O$
7k	3-CF_3	(*Z*)-CH=CH	2	229-231	89	95% EtOH	A	$C_{16}H_{21}F_3N_2 \cdot 2HCl \cdot H_2O$
7l	H	(*E*)-CH=CH	2	258-262	87	abs EtOH	A	$C_{15}H_{22}N_2 \cdot 2HCl \cdot 0.25H_2O$
7m	3-CF_3	(*E*)-CH=CH	2	249-251	95	EtOH/Et_2O	A	$C_{16}H_{21}F_3N_2 \cdot 2HCl$

[a] Melting points are for the dihydrochloride salts, except as otherwise noted. [b] Capitol letters refer to methods A-E in the Experimental Section. [c] All compounds analyzed for C, H, N, and, where present, Cl and are within ±0.4% of the calculated values. [d] Hydrogen oxalate salt. [e] Literature[28] mp 131-133 °C. [f] Literature[29] mp 151-152 °C.

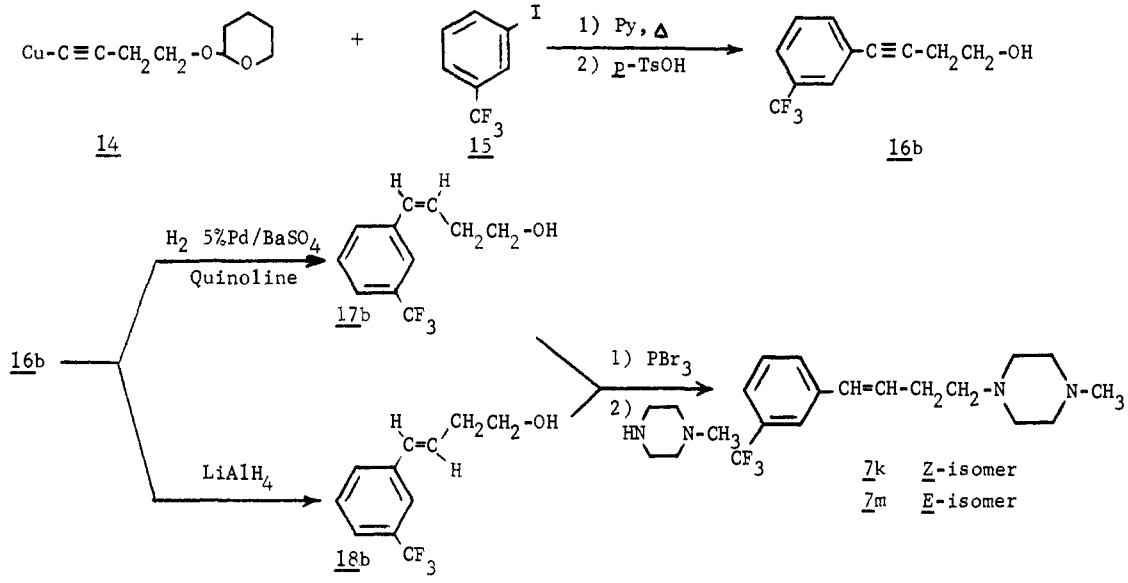
These compounds possess an aromatic ring and a terminal amine function (usually a methylpiperazine) common to, but lack the tricyclic structure of, **1** and **2**. The distance between the ring and the amine function is varied by using a two- to four-membered unbranched chain, while the electronic influence of this side chain is to be investigated by incorporating a heteroatom or by introducing unsaturation. Using such an approach, it should be possible to determine whether or not the entire tricyclic structure of the neuroleptics is necessary for dopamine antagonism.

Chemistry. Most of the final products were prepared by alkylation of 1-methylpiperazine with the appropriate alkyl halide (Scheme I). Several of these halides were commerically available, while the remainder could be easily synthesized in a few steps. 2-Chlorophenylacetic acid, for example, was reduced with $LiAlH_4$ to the alcohol **4**, which afforded **6b** upon treatment with PBr_3. 4-Phenylbutanol (**5**) was brominated in the same manner to give **6e**. Acylation of 1-methylpiperazine with 2-chlorcinnamoyl chloride (**8**), followed by the reduction of the cinnamamide **9**, afforded **7d**.

It was initially envisioned that compounds **7f–i** could be prepared by alkylation of the appropriate phenol or aniline with **10**;[14] reduction of the resultant amide would yield the desired products. Although **10** was prepared in nearly quantitative yield, it was prone to formation of hygroscopic carbonate salts upon exposure to the atmosphere and, as a result, was quite difficult to handle. Compounds **7f** and **7g** were synthesized by alkylation of 1-methylpiperazine with **6f** and **11**, respectively. Acylation of aniline and 3-chloroaniline with 3-bromopropionyl

(14) Caldwell, A. G.; Wells, L. P.; Barrett, P. A. German Patent 1 139 504, 1962; *Chem. Abstr.* **1963**, *58*, 13968*b*.

Scheme II



chloride to the bromo amides **12** and **13**, with subsequent amination (to **12a** and **13a**) and $LiAlH_4$ reduction, afforded **7h** and **7i**.

The unsaturated analogues **7j–m** were prepared via the acetylenic alcohol intermediates **16a** and **16b** (Scheme II). Treatment of the Grignard salt of phenylacetylene with ethylene oxide as reported by Faucounau[15] afforded **16a**. The trifluoromethyl analogue **16b** was prepared by allowing the copper(I) salt of a tetrahydropyran-blocked butynol, **14**, to react with 3-(trifluoromethyl)iodobenzene. Compound **16b** afforded the cis alcohol **17b** upon catalytic reduction using a poisoned 5% $Pd/BaSO_4$ catalyst, while reduction with $LiAlH_4$ gave the trans isomer **18b**. Compounds **17a** and **18a** were prepared in the same manner. The alcohols were brominated to give **19a,b** and **20a,b** which were aminated to yield the desired unsaturated aralkenylpiperazine derivatives **7j–m**.

Results and Discussion

Each of the final products, **7a–p**, was evaluated for its dopamine antagonist activity in the superfused rabbit ear artery preparation; the results are summarized in Table II. Steinsland and Hieble[8] have shown a good correlation between K_B values determined for several neuroleptic agents in this assay and the K_i values for inhibition of [^{3}H]haloperidol binding in calf brain homogenates.[7] For example, haloperidol was found to have a K_i of 0.0014 μM in the former assay and a K_B of 0.0014 μM in the latter assay.[8] Although Burt et al.[7] report a K_i of 0.01 μM for chlorpromazine, the K_B for this compound is 1.0 μM. Chlropromazine may have an intefering noradrenergic response in the rabbit ear artery preparation; therefore, clozapine (K_B = 10 μM) has been used as the standard. There was no evidence of adrenergic interference by compounds **7a–p**.

Reviewing the data in Table II, it can be seen that the phenethyl analogue **7a** is inactive and that the addition of the 2-chloro substituent (i.e., **7b**) has no effect on dopamine antagonist activity. Surprisingly, the phenylpropyl compound **7c** possesses some activity; yet, its 2-chloro analogue is inactive. The three dimethylamino analogues **7n–p** are all inactive. More interesting are the data from the derivatives which possess a four-membered chain (i.e., **7e–i**), in that these compounds more closely resemble the

Table II. Data on Dopamine Antagonism

no.	X	R	n	K_B, μM[a]
7a	CH_2	H	1	inactive[b]
7b	CH_2	2-Cl	1	inactive[b]
7c	CH_2	H	2	8 (±2.3), N = 4
7d	CH_2	2-Cl	2	inactive[b]
7e	CH_2	H	3	inactive[c]
7f	O	H	3	~900
7g	O	3-Cl	3	29 (±3.0), *N* = 4
7h	NH	H	3	38 (±5.0), *N* = 4
7i	NH	3-Cl	3	0.75 (±0.43), *N* = 6
7j	(*Z*)-CH=CH	H	2	1.2 (±0.60), *N* = 6
7k	(*Z*)-CH=CH	3-CF_3	2	0.72 (±0.36), *N* = 6
7l	(*E*)-CH=CH	H	2	120 (±9.0), *N* = 6
7m	(*E*)-CH=CH	3-CF_3	2	48 (±6.0), *N* = 6
7n	CH_2	H	2	inactive[c]
7o	CH_2	2-OMe	2	inactive[c]
7p	CH_2	3-OMe	2	inactive[c]

[a] Clozapine, K_B = 10 μM; K_B values are followed by standard deviation (in parentheses) and number of determinations (*N*). [b] Inactive up to 10 μM. [c] Inactive up to 100 μM.

structure of the phenothiazines. The four-carbon chain derivative **7e** is inactive, while its phenoxy counterpart **7f** is only very weakly active as a dopamine antagonist. Chlorination of **7f** meta to the side chain to give **7g** results in a 30-fold increase in activity. Similar results are observed when the oxygen is replaced with a nitrogen atom to give **7h** and **7i**, respectively. Compounds **7j–m**, which are related to the thioxanthenes, **2**, also exhibit an interesting spectrum of activity. With respect to the unsubstituted compounds, the cis isomer **7j** is 100-fold more active than its trans isomer **7l**. In the pair of meta-substituted trifluoromethyl analogues, again the cis isomer **7k** is more active (in this case, by approximately 70-fold) than its isomer **7m**.

In attempting to correlate the many types of structures which exhibit neuroleptic activity, Janssen has noted several structural categories for which the general formula Ar–N–C–C–C–N may be written.[16] Pletscher and Kyburz[17] have somewhat expanded this idea and have suggested minimal structural requirements necessary (but not sufficient) for dopamine antagonism. For the most part, compounds **7h–m** meet these requirements and, indeed,

(15) Faucounau, L. *C. R. Hebd. Seances Acad. Sci.* **1934**, *199*, 605.

(16) Janssen, P. A. G. *Int. Encyl. Pharmacol. Ther.* **1973**, *1*, Chapter 2.

(17) Pletscher, A.; Kyburz, E. *Schizophr. Today* **1976**, 183–200.

do possess activity as dopamine antagonists. Furthermore, these compounds follow the general SAR established for known dopamine antagonists; e.g., (a) addition of an electron-withdrawing group meta to the side chain enhances activity and (b), with respect to thioxanthenes, the cis isomer is more active than the trans isomer. Some of these molecular subfragments act as dopamine antagonists and, as such, support the minimal requirements proposed for dopamine antagonism. Although compounds **7i–k** are more active than clozapine, their activity is still much less than that of, for example, haloperidol by several orders of magnitude.

Experimental Section

Chemistry. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds are consistent with their IR, NMR, and mass spectral data. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer and ^1H NMR spectra were determined on a Perkin-Elmer R-24 spectrometer, using Me_4Si as an internal standard. Mass spectra were obtained on a Finnigan 4015 GC/MS at 70 eV. Vapor-phase chromatography (VPC) was conducted on an Aerograph 700 Autoprep using a 6 ft × 0.25 in. glass column packed with 10% Apiezon L on 80–100 mesh Chromosorb W, with column temperature maintained at 200 °C for prepartion of analytical samples. With respect to compounds where mixtures of *E* and *Z* isomers are possible, all final products were found to give single peaks upon VPC analysis. Microanalysis were performed for all new compounds by Atlantic Microlab, Atlanta, GA, and results are within ±0.4% of the calculated values.

2-(2-Chlorophenyl)ethanol (4). A solution of 2-chlorophenylacetic acid (2.0 g, 12 mmol) in dry THF (30 mL) was added dropwise over a 15-min period to a stirred, ice-cooled suspension of $LiAlH_4$ (0.34 g, 10 mmol) in dry THF (20 mL). The reaction mixture was stirred at room temperature for 0.5 h and then heated at reflux for 2 h. After the mixture cooled to 0 °C, a 20% solution of H_2O in THF (5 mL) was added in a dropwise manner. The mixture was filtered, the filtrate was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give the crude product as a yellow oil. Distillation afforded 1.6 g (88%) of 4 as a colorless oil, bp 58–61 °C (0.08 mm) [lit.[18] 84–85 °C (0.3 mm)].

1-Bromo-4-phenylbutane (6e). A solution of phosphorus tribromide (0.95 g, 4 mmol) in benzene (10 mL) was added in a dropwise manner, over a 5-min period, to a stirred ice-cooled solution of 4-phenylbutanol (1.5 g, 10 mmol) in benzene (10 mL). The mixture was stirred at 0 °C for 1 h, heated at reflux for 3 h, cooled to 0 °C, and 5 g of ice was added. The organic layer was separated, washed twice with H_2O (10 mL), and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give a yellow oil. Distillation gave 1.14 g (53%) of **6e** as a colorless oil, bp 63–68 °C (0.5 mm) [lit.[19] bp 132–134 °C (12 mm)].

2-(2-Chlorophenyl)ethyl Bromide (6b). Compound 4 (1.1 g, 7 mmol) was brominated in the same manner employed for the preparation of **6e** to yield 1.25 g (78%) of **6b** as a pale yellow liquid, bp 47–49 °C (0.11 mm) [lit.[20] bp 113–115 °C (10 mm)].

Method A. 2-(4-Methylpiperazino)-1-phenylethane (7a). A solution of phenethyl bromide (1.85 g, 10 mmol) and *N*-methylpiperazine (2.0 g, 20 mmol) in dry THF (50 mL) was heated under reflux for 48 h. After the solution cooled, the precipitated piperazine hydrobromide was removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. Distillation afforded 2.2 g (97%) of **7a** as a colorless oil, bp 80–85 °C (0.6 mm). A small sample was dissolved in anhydrous Et_2O and treated with gaseous HCl at 0 °C to afford the HCl salt. Recrystallization from absolute EtOH gave a quantitative yield of the dihydrochloride as white leaflets, mp 279–280 °C. Anal. ($C_{13}H_{20}N_2 \cdot 2HCl$) C, H, N.

Method B. 3-(2-Chlorophenyl)-1-(4-methylpiperazino)propane (7d). A solution of **9** (1.0 g, 3.77 mmol) in anhydrous Et_2O (25 mL) was added over a 10-min period to a stirred, ice-cooled suspension of $LiAlH_4$ (0.29 g, 7.54 mmol) under an atmosphere of dry N_2. The stirred mixture was heated at reflux for 24 h. After the mixture cooled to 0 °C, $Na_2SO_4 \cdot 10H_2O$ was added in small portions until evolution of H_2 ceased. The mixture was filtered, and the filtrate was dried ($MgSO_4$) and evaporated to give 0.65 g (68%) of a yellow oil. The oil was dissolved in anhydrous Et_2O and treated with HCl gas to yield the dihydrochloride salt of **7d**. Recrystallization from absolute EtOH gave 0.83 g (68%) of product, mp 245–248 °C. Anal. ($C_{14}H_{21}ClN_2 \cdot 2HCl$) C, H, N, Cl.

Method C. 1-(Dimethylamino)-3-(3-methoxyphenyl)propane (7p). A solution of 1-bromo-3-(3-methoxyphenyl)propane (1.15 g, 3 mmol) and dimethylamine (1.08 g, 24 mmol) in 95% EtOH (25 mL) was heated in a Parr bomb (45-mL capacity) in an oil bath (100 °C) for 5 h. After the solution cooled, the solvent was evaporated under reduced pressure and aqueous NaOH (20%, 10 mL) was added to the crude residue. The mixture was extracted with Et_2O (3 × 25 mL); the combined Et_2O fractions were dried (Na_2SO_4) and evaporated. Distillation yielded 0.72 g (75%) of **7p**, bp 72–73 °C (0.05 mm). The hydrochloride salt was prepared by bubbling dry HCl gas through an anhydrous Et_2O solution of **7p**, mp 122–124 °C after recrystallization from absolute EtOH. Anal. ($C_{12}H_{19}NO \cdot HCl$) C, H, N, Cl.

Method D. *N*-Phenyl-3-(4-methylpiperazino)-1-aminopropane (7h). A solution of **12a** (1.0 g, 4 mmol) in dry THF (25 mL) was added dropwise over a 10-min period to a stirred, ice-cooled suspension of $LiAlH_4$ (0.17 g, 4.5 mmol) in dry THF (10 mL). The mixture was heated at reflux for 3 h and cooled, and $Na_2SO_4 \cdot 10H_2O$ was added in small portions until evolution of H_2 ceased. The mixture was stirred at room temperature for 0.5 h and filtered, and the filtrate was dried ($MgSO_4$). Evaporation of solvent under reduced pressure gave 0.76 g (81%) of **7h** as a yellow oil. This was dissolved in anhydrous Et_2O and added to a saturated ethereal solution of oxalic acid. The resulting white precipitate was washed with ether and recrystallized from glacial HOAc to give white powdery crystals, mp 210–212 °C. Anal. ($C_{14}H_{23}N_3 \cdot 3C_2H_2O_4 \cdot H_2O$) C, H, N.

Method E. 1-(3-Chlorophenoxy)-3-(4-methylpiperazino)propane (7g). A solution of **11** (3.0 g, 15 mmol) and *N*-methylpiperazine (3.0 g, 30 mmol) in dioxane (25 mL) was refluxed for 3 h. The brown solution was cooled and filtered, and the solvent was evaporated under reduced pressure. The resultant yellow oil was dissolved in aqueous HCl (5%, 50 mL) and washed twice with Et_2O (50 mL). The aqueous phase was basified to pH 10 by the careful addition of aqueous NaOH (10%) and was extracted twice with Et_2O (50 mL); the ether portions were combined and dried ($Na_2SO_4/MgSO_4$). Evaporation of solvent under reduced pressure gave 1.69 g (43%) of **7g** as a pale yellow liquid. A portion was dissolved in anhydrous Et_2O and treated with gaseous HCl at 0 °C to give, after recrystallization from absolute EtOH, white platelets, mp 245–248 °C. Anal. ($C_{14}H_{21}ClN_2O \cdot 2HCl$) C, H, N, Cl.

1-[3-(2-Chlorophenyl)propenoyl]-4-methylpiperazine (9). A solution of 3-(2-chlorophenyl)propenoyl chloride[27] (2.0 g, 10 mmol) in anhydrous Et_2O (25 mL) was added dropwise over a 5-min period to a stirred, ice-cooled solution of 1-methylpiperazine (2.0 g, 20 mmol) in ahydrous Et_2O (25 mL). The stirred mixture was heated at reflux for 3 h, cooled, and filtered. Evaporation of the filtrate under reduced pressure gave an orange-yellow solid, which was recrystallized from ligroin (bp 60–90 °C) to yield 1.65 g (62%) of orange flakes, mp 91–92.5 °C. Anal. ($C_{14}H_{17}ClN_2O$) C, H, N, Cl.

1-Chloro-3-(3-chlorophenoxy)propane (11). A mixture of 3-chlorophenol (5.0 g, 39 mmol), 1-bromo-3-chloropropane (6.07 g, 39 mmol), and K_2CO_3 (5.52 g, 40 mmol) in acetone (50 mL) was heated at reflux for 10 h. After cooling, the mixture was filtered and the filtrate evaporated under reduced pressure to afford a yellow oil. This oil was dissolved in Et_2O (30 mL) and washed once with aqueous NaOH (10%, 25 mL) and twice with H_2O (25 mL). After drying ($Na_2SO_4/MgSO_4$), the solvent was evaporated under reduced pressure to give a pale yellow oil. Distillation gave 4.91 g (62%) of **11** as a colorless liquid, bp 70–73 °C (0.1 mm). Anal. ($C_9H_{10}Cl_2O$) C, H, Cl.

***N*-Phenyl-3-bromopropionamide (12).** A solution of 3-bromopropionyl chloride (2.0 g, 12 mmol) in anhydrous Et_2O (50

(18) Bunnett, J.; Skorcz, J. *J. Org. Chem.* **1962**, *27*, 3836.
(19) Cherkasov, L.; Balyan, K.; Kormer, V. *Zh. Org. Khim.* **1966**, *2*, 1934; *Chem. Abstr.* **1967**, *66*, 75760u.
(20) Barnes, R.; Konort, M. *J. Am. Chem. Soc.* **1953**, *75*, 303.

mL) was added in a dropwise manner to a stirred, ice-cooled solution of aniline (2.23 g, 24 mmol) in anhydrous Et_2O. The mixture was stirred at room temperature for 2 h and filtered, and the filtrate was evaporated to dryness under reduced pressure. The resultant yellow solid was dissolved in $CHCl_3$ (100 mL) and was washed twice with aqueous HCl (5%, 100 mL). The organic portion was dried ($MgSO_4$) and the solvent was evaporated to yield a white product. Recrystallization from H_2O gave 2.25 g (85%) of **12** as white needles, mp 120–121 °C (lit.[21] 119–120 °C).

***N*-(3-Chlorophenyl)-3-bromopropionamide (13).** Compound **13** was prepared in the same manner as **12**. Recrystallization of the crude product from ligroin (bp 60–90 °C) gave a 95% yield of **13** as small white needles, mp 73–75 °C. Anal. ($C_9H_9BrClNO$) C, H, N.

***N*-Phenyl-3-(4-methylpiperazino)propionamide (12a).** A solution of **12** (1.5 g, 6.6 mmol) and 1-methylpiperazine (1.32 g, 13.2 mmol) in dry THF (25 mL) was heated at reflux for 10 h. After cooling, the mixture was filtered and the solvent was evaporated under reduced pressure to yield a crude product. Recrystallization from ligroin (bp 60–90 °C) gave 1.54 g (94%) of **12a** as white needles, mp 90–92 °C. Anal. ($C_{14}H_{21}N_3O$) C, H, N.

***N*-(3-Chlorophenyl)-3-(4-methylpiperazino)propionamide (13a).** Compound **13a** was prepared in the same manner as **12a** but was purified by passing a solution of **13a** and EtOAc through a column packed with alumina (80–200 mesh). Evaporation of the solvent resulted in a crude yellow oil which solidified on standing. Recrystallization from ligroin (bp 60–90 °C) gave 74% of **13a** as small white needles, mp 101–102 °C. The dihydrochloride salt has been previously reported;[22] however, in our hands, exposure of **13a** to HCl resulted in extensive decomposition. Consequently, **13a** was characterized as the free base. Anal. ($C_{14}H_{20}ClN_3O$) C, H, N, Cl.

Copper(I) 4-[(Tetrahydropyranyl)oxy]-1-butynide (14). Over a period of 10 min, and under an N_2 atmosphere, $NH_2OH{\cdot}HCl$ (2.76 g, 40 mmol) was added to a stirred solution of $CuSO_4{\cdot}5H_2O$ (5 g, 20 mmol) and NH_4OH (20 mL) in H_2O (80 mL) at 0 °C. A solution of 4-[(2-tetrahydropyranyl)oxy]-1-butyne[23] (3.08 g, 20 mmol) in 95% EtOH (100 mL) was added with rapid swirling. After the addition of H_2O (100 mL), rapid swirling was continued for another 10 min. The yellow precipitate was filtered, washed successively with H_2O, absolute EtOH, and anhydrous Et_2O, and was dried in a vacuum dessicator at 25 °C for 2 h. The bright yellow solid product, 4.25 (98%), which decomposed violently at 158 °C, was used without further purification.

3-(Trifluoromethyl)-1-iodobenzene (15). A solution of sodium nitrite (3.0 g, 43 mmol) in concentrated H_2SO_4 (30 mL) was added in a dropwise manner, over a period of 10 min, to a stirred solution of 3-(trifluoromethyl)aniline (6.44 g, 40 mmol) in 85% phosphoric acid (70 mL) at −5 °C. Stirring was continued at −5 °C for 30 min, at which time urea (2.0 g) was added and the entire solution was poured rapidly onto a mixture of KI (8 g) and ice. The mixture was allowed to stand overnight and was then extracted twice with Et_2O (250 mL). The combined Et_2O extract was stirred with aqueous NaOH (8 N, 50 mL) until most of the dark color disappeared. The organic phase was separated, washed with H_2O (200 mL), and dried ($Na_2SO_4/MgSO_4$), and the solvent was evaporated under reduced pressure to give a dark oil. Distillation yielded 7.56 g (69%) of **15** as a clear yellow liquid, bp 80–83 °C (25 mm) [lit.[24] 74–76 °C (20 mm)].

4-Phenyl-3-butyn-1-ol (16a). A solution of ethyl bromide (5.45 g, 50 mmol) in anhydrous Et_2O (20 mL) was added dropwise to a stirred mixture of Mg turnings (1.32 g, 55 mmol) and a catalytic amount of I_2 in anhydrous Et_2O (100 mL). After the mixture stirred for 30 min, a solution of phenylacetylene (5.1 g, 50 mmol) in ahydrous Et_2O (50 mL) was added in a dropwise manner, and the mixture was refluxed for 1 h. The stirred mixture was cooled to 0 °C, and a solution of ethylene oxide (15 g, 340 mmol) in anhydrous Et_2O (25 mL) was added over a 5-min period. After the mixture was stirred at 0 °C for 1 h and at room temperature for 30 min, a saturated solution of NH_4Cl was added until precipitation of magnesium salts was complete. The mixture was filtered, and the filtrate was dried ($Na_2SO_4/MgSO_4$) and evaporated under reduced pressure. Distillation gave 2.96 g (41%) of **16a** as a colorless liquid, bp 93–97 °C (0.54 mm) [lit.[15] bp 147 °C (16 mm)].

4-[3-(Trifluoromethyl)phenyl]-3-butyn-1-ol (16b). A solution of **14** (2.17 g, 10 mmol) and **15** (2.72 g, 10 mmol) in pyridine (25 mL) was refluxed for 15 h under an atmosphere of N_2. After cooling, the mixture was poured into H_2O (50 mL) and stirred for 15 min. The upper green layer was decanted and the brown precipitate was extracted twice with Et_2O (25 mL). The combined extracts were washed with aqueous HCl (1 N, 25 mL), aqueous Na_2CO_3 (5%, 25 mL), and H_2O (25 mL) and dried (Na_2SO_4), and the solvent was evaporated to give a brown oil. This was dissolved in absolute EtOH (25 mL) with *p*-toluenesulfonic acid (0.06 g, 0.3 mmol) and heated at reflux for 3 h. After the mixture cooled, K_2CO_3 (0.2 g, 1.4 mmol) was added and the mixture was stirred for 15 min. The mixture was filtered and the solvent evaporated from the filtrate to give a brown oil. Distillation yielded 0.71 g (33% overall) of **16b** as a colorless liquid, bp 84–89 °C (0.4 mm). The analytical sample was prepared by preparative VPC. Anal. ($C_{11}H_9F_3O$) C, H.

(*Z*)-4-Phenyl-3-buten-1-ol (17a). A solution containing **16a** (1.0 g, 7.0 mmol), synthetic quinoline (4 drops), and 5% Pd on $BaSO_4$ (0.1 g) in absolute EtOH was vigorously stirred under an atmosphere of H_2 on a Brown hydrogenation apparatus for 1.5 h. The mixture was then filtered and the solvent evaporated under reduced pressure to give a yellow oil. Distillation gave 0.9 g (88%) of **17a** as a colorless liquid, bp 65–66 °C (0.04 mm) [lit.[25] bp 88 °C (0.6 mm)].

(*Z*)-4-[3-(Trifluoromethyl)phenyl]-3-buten-1-ol (17b). Compound **17b** was prepared from **16b** by the same procedure as **17a**, except that the hydrogenation was allowed to proceed for 16 h. Distillation of the crude product gave 97% of **17b** as a colorless oil, bp 68–74 °C (0.05 mm). The analytical sample was prepared by preparative VPC. Anal. ($C_{11}H_{11}F_3O$) C, H.

(*E*)-4-Phenyl-3-buten-1-ol (18a). A solution of **16a** (2.75 g, 19 mmol) in dry THF (25 mL) was added dropwise over a 10-min period to a stirred, ice-cooled suspension of $LiAlH_4$ (2.20 g, 56 mmol) in dry THF (25 mL). The mixture was then heated at reflux for 15 h, cooled to 0 °C, and $Na_2SO_4{\cdot}10H_2O$ was added in small portions until evolution of H_2 ceased. The mixture was filtered and dried ($Na_2SO_4/MgSO_4$), and the solvent was evaporated under reduced pressure to give a yellow oil. The oil was dissolved in benzene and chromatographed on a column packed with Silicar CC-7 (Mallinckrodt), eluting with benzene followed by EtOAc. Evaporation of solvent from the EtOAc fraction followed by distillation gave 2.05 g (74%) of **16a** as a colorless liquid, bp 81–82 °C (0.15 mm) [lit.[25] bp 96 °C (0.6 mm)].

(*E*)-4-[3-(Trifluoromethyl)phenyl]-3-buten-1-ol (18b). Compound **18b** was prepared from **16b** by the same procedure used for **18a** to give 70% of a clear liquid, bp 76–82 °C (0.15 mm). The analytical sample was prepared by preparative VPC. Anal. ($C_{11}H_{11}F_3O$) C, H.

(*Z*)-4-Bromo-1-phenyl-1-butene (19a). A solution of PBr_3 (2.71 g, 10 mmol) in benzene (20 mL) was added dropwise over a 10-min period to a stirred, ice-cooled solution of **17a** (3.0 g, 20 mmol) in benzene (20 mL). The stirred solution was refluxed for 3 h and then cooled to 0 °C, and ice (5.0 g) was added to the reaction mixture. The aqueous layer was separated and extracted twice with benzene (20 mL), the organic layers were combined and dried ($Na_2SO_4/MgSO_4$), and the solvent was evaporated under reduced pressure to give a cloudy, colorless oil. Distillation yielded 2.35 g (55%) of **19a** as a clear, colorless liquid, bp 49–51 °C (0.05 mm). Anal. ($C_{10}H_{11}Br$) C, H.

(*Z*)-4-Bromo-1-[3-(trifluoromethyl)phenyl]-1-butene (19b). Compound **19b** was prepared from **17b** by the same procedure as for **19a** to give 71% of a colorless liquid, bp 67–69 °C (0.05 mm). Anal. ($C_{11}H_{10}BrF_3$) C, H.

(21) Johnson, H. W.; Schweitzer, M. *J. Org. Chem.* **1961**, *26*, 3666.
(22) Klosa, J.; German Patent 1 093 800, 1960; *Chem. Abstr.* **1961**, *55*, 19966.
(23) Jones, E. R. H.; Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 230.
(24) Kwatra, M.; Simon, D.; Salvador, R.; Cooper, P. *J. Med. Chem.* **1978**, *21*, 253.
(25) Carr, J.; Kirby, P.; Goodrow, M.; Durham, H.; Hass, D.; Boudreau, J. *J. Med. Chem.* **1972**, *15*, 1231.

(E)-4-Bromo-1-phenyl-1-butene (20a). Prepared from **18a** by the same procedure used for **19a** to give 58% of a colorless oil, bp 76–82 °C (0.08 mm) [lit.[26] bp 144–145 °C (10 mm)].

(E)-4-Bromo-1-[3-(trifluoromethyl)phenyl]-1-butene (20b). Compound **20b** was prepared from **18b** by the same procedure used for **20a** to give 49% of a clear yellow liquid, bp 65–67 °C (0.07 mm). Anal. ($C_{11}H_{10}BrF_3$) C, H.

Pharmacology. The isolated perfused rabbit ear artery preparation described by Steinsland et al.[8] was used in these studies. In brief, male rabbits (2–4 kg) were sacrificed by a blow to the head, and a 2–4 cm portion of the central ear artery was disected free at the base of the ear, cannulated at both ends, and mounted in a perfusion chamber immersed in a bath maintained at 37 °C. Perfusion flow was delivered at a constant rate (2 mL/min) from a polystaltic pump. Changes in the intraluminal flow pressure were measured with a Statham P23AA pressure transducer and recorded on a physiograph equipped with strip recorder. Both the intraluminal and extraluminal perfusion fluid was oxygenated in Krebs bicarbonate solution. All test compounds were introduced into the extraluminal flow of perfusate following an initial 2-h equilibration period. The periarterial sympathetic nerves were excited by a field stimulation produced by rectangular pulses of 1-ms duration and a supramaximal voltage (80–90 V), delivered from a Grass Model S-8 stimulator, and applied through platinum electrodes mounted at the top and bottom of the perfusion chamber. The dissociation contants (K_B values) were calculated using the formula K_B = antagonist concentration/(dose ratio −1), where the dose ratio represents the concentration of dopamine required to produce 50% inhibition of the constrictor response to nerve stimulation in the presence of antagonist divided by the dopamine concentration required to produce the same degree of inhibition with no antagonist present.

(26) Hanack, M.; Kang, S.; Haeffner, J.; Goerler, K. *Justus Liebigs Ann. Chem.* **1965**, 690, 98.
(27) Weiler, G. *Chem. Ber.* **1923**, *56B*, 1481.
(28) Bavin, P. M. G.; Ganellin, C. R.; Loynes, J. M.; Miles, P. D.; Ridley, H. F. *J. Med. Chem.* **1966**, *9*, 790.
(29) Yoshida, N.; Omoto, M.; Inoi, T. *Yakugaku Zasshi* **1958**, *78*, 183; *Chem. Abstr.* **1958**, *52*, 10919.

Synthesis and Pharmacological Evaluation of Sulfonium Analogues of Dopamine: Nonclassical Dopamine Agonists

Karen Anderson, Alice Kuruvilla, Norman Uretsky, and Duane D. Miller*

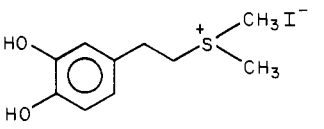
Divisions of Medicinal Chemistry and Pharmacognosy and of Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210. *Received November 17, 1980*

In order to test whether the nitrogen/ammonium moiety in the dopamine molecule is required for dopaminergic activity, we have synthesized two sulfonium analogues of dopamine and tested them for biological activity in an in vivo and in an in vitro system. These analogues have provided a means of investigating (1) the ability of the sulfonium function to serve as a bioisostere for the dopamine amino group and (2) whether charged molecules have the ability to bind to dopamine receptors. Both sulfonium analogues, **1** and **2**, as well as dopamine, when injected directly into the striatum of rats, previously lesioned unilaterally with 6-hydroxydopamine (6-OHDA), produced circling behavior. The potency of the sulfonium analogues was approximately one-tenth that of dopamine. The effects of all three compounds on circling were inhibited by the dopamine antagonist haloperidol. In addition, both sulfonium analogues inhibited the high affinity binding of radiolabeled dopamine to a crude membrane fraction prepared from the striatum. This study suggests that the nitrogen atom found in the dopamine molecule is not essential for dopaminergic activity, since the nitrogen can be replaced by a sulfonium functional group for this activity.

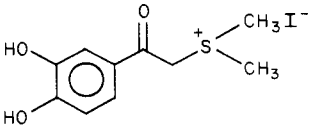
In the late 1950's Blaschko[1] suggested that dopamine, well known as a precursor of norepinephrine and epinephrine, might have a physiological role of its own. Since that time, dopamine has been shown to be a neurotransmitter present in mammalian brain and periphery, and a large amount of research on the chemistry, physiology, and pharmacology of this substance has been reported. Abnormal dopaminergic transmission has been implicated in a wide variety of diseases, including Parkinson's disease, mental disorders, Huntington's disease, tardive dyskinesia, and neuroendocrine disorders associated with prolactin control.[2]

The structural requirements for compounds producing dopaminergic activity have been the subject of considerable study.[3-6] A variety of studies have been directed toward understanding the conformational and configurational requirements for dopamine receptors. Among the ligands showing dopaminergic activity, the structural requirements for nitrogen substitution do not seem highly stringent, since primary, secondary, and tertiary amines have shown dopaminergic activity.

The present study is directed toward a better understanding of what the basic structural requirements are for dopaminergic activity. We were interested in knowing if the nitrogen atom of dopamine could be replaced with other heteroatoms and still retain dopamine agonist activity. The synthesis and preliminary biological investigations including dopamine binding and behavioral studies of the two sulfonium analogues of dopamine, **1** and **2**, represent our initial effort in this area.



1



2

Chemistry. The synthesis of sulfonium analogue **1** is outline in Scheme I. Following esterification of piperonylic acid, the resulting ester was treated with the lithium salt of dimethyl sulfoxide to give keto sulfide **4**. Reduction of

(1) H. Blaschko, *Experientia*, **13**, 9 (1957).
(2) P. Seeman, M. Titeler, J. Tedesco, P. Weinreich, and D. Sinclair, *Adv. Biochem. Psychopharmacol.*, **19**, 167 (1978).
(3) J. McDermed, *Annu. Rep. Med. Chem.*, **14**, 12 (1979).
(4) D. Miller, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2394 (1978).
(5) J. G. Cannon, *Adv. Neurol.*, **9**, 177 (1975).
(6) D. C. Remy and G. E. Martin, *Annu. Rep. Med. Chem.*, **15**, 12 (1980).

0022-2623/81/1824-0683$01.25/0